



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



⑪ Publication number: **0 444 000 A2**

⑫

## EUROPEAN PATENT APPLICATION

⑯ Application number: **91850031.5**

⑮ Int. Cl.<sup>5</sup>: **A61K 31/70, A61K 9/48,  
A61K 47/02, A61K 47/22**

⑯ Date of filing: **12.02.91**

⑯ Priority: **22.02.90 US 483572**

⑯ Inventor: **Demopoulos, Harry Byron  
24 Sycamore Road  
Scarsdale, N.Y. 10583 (US)**

⑯ Date of publication of application:  
**28.08.91 Bulletin 91/35**

⑯ Representative: **Kristiansen, Alf P. et al  
Albijn West AB Stora Nygatan 15 Box 142  
S-401 22 Göteborg (SE)**

⑯ Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

⑯ Applicant: **Health Maintenance Programs, Inc.  
7 Westchester Plaza  
Elmsford, New York 10523 (US)**

⑯ **Storage-stable glucosamine sulphate oral dosage forms and methods for their manufacture.**

⑯ The present invention relates to storage-stable glucosamine sulphate oral dosage forms including calcium carbonate and ascorbic acid. The invention also relates to the methods of production of these oral dosage forms.

EP 0 444 000 A2

Jouve, 18, rue Saint-Denis, 75001 PARIS

## STORAGE-STABLE GLUCOSAMINE SULPHATE ORAL DOSAGE FORMS AND METHODS FOR THEIR MANUFACTURE

The present invention relates to the field of storage-stable glucosamine sulphate oral dosage forms and methods for their manufacture.

Glucosamine sulphate is a well known and extremely important substance in the treatment of rheumatic fever, arthritic and arthrosic complaints, both in the acute and chronic forms, and, generally, of all pathological conditions originating from metabolic disorders of the osteo-articular tissue. See U.S. Patent No. 3,683,076, and United Kingdom Patent No. 1,056,331. See also I. Setnikar et al., "Pharmacokinetics of Glucosamine in the Dog and in Man," *Arzenimittelforschung*, April 1986, 36(4) pp. 729-35.

Glucosamine, used in the form of the salt with hydrochloric, sulphuric, phosphoric, or other biocompatible acids, is known to have an anti-inflammatory effect when taken orally or parenterally. Tapadinhas et al., *Pharmatherapeutica*, 3(3), 157-168 (1982).

The synthesis of glucosamine sulphate was described by Breuer in 1898 (Chem. Ber. 31, 2197) and an industrial method is the subject of U.K. Patent No. 1,056,331. U.S. Patent No. 3,683,076 and Swiss Patent No. 525,861.

However, glucosamine sulphate has several properties which render its packaging problematic. Specifically, glucosamine sulphate is highly hygroscopic in nature and the amino group oxidizes readily.

These unfavorable properties give rise to difficulties and limitations in the practical use of glucosamine sulphate. For example, oral forms, such as tablets or capsules, require anti-oxidants, such as sodium hyposulphite, to be present in their formulations. Generally, these substances, although blocking the oxidation of the amino group, do not solve the problem of the hygroscopic nature of the sulphate. This necessitates the preparation of these forms in environments with a relative humidity not greater than 30%, and even then, the results are unsatisfactory. Similar comments apply to rectal forms (suppositories) which, even if kept under dry, refrigerated conditions, degrade with considerable rapidity.

U.S. Patent No. 4,642,340 suggests that it is possible to stabilize glucosamine sulphate by the formation of a mixed salt thereof with sodium chloride.

Published European Application EP 214, 642, published March 10, 1987, also suggests the use of a stabilizing salt, but discloses the use of  $MgCl_2$ ,  $NaBr$  and  $KBr$  instead of  $NaCl$ .

Furthermore, it is known that ascorbic acid may be used to prevent the oxidation of materials such as compositions including cyclo-(N-methyl-Ala-Tyr-D-Trp-Lys-Val-Phe) and a selected non-steroidal anti-inflammatory drug. See U.S. Patent No. 4,474,766.

U.S. Patent No. 4,590,067 relates to a treatment of periodontal disease and describes a composition for topical applications, including a calcium source, glucosamine or other simple sugars; or amino sugar having anti-inflammatory activity, ascorbic acid and tyrosine, phenylalanine or other precursor or stimulant of epinephrine or nor-epinephrine production. Bone meal or the equivalent serves as a source of calcium for tooth regeneration, as a general cleansing agent, and as a filler. Equivalent substances include biologically compatible calcium salts, representative of which are calcium gluconate, calcium carbonate, tricalcium and dicalcium phosphate, dolomite and the like.

15 The anti-inflammatory substance may be selected from the amino sugars, glucosamine, D-mannosamine, D-galactosamine, their biocompatible acid addition salts, glucosamine-6-phosphate, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine, UDP-N-acetylglucosamine; the sugars 2 deoxy-D-glucose, 2-deoxy-D-galactose and mannose; and the amino acids cysteine, creatine, creatinine, L-tryptophan, valine, alanine, glycine, glutamine, aspartic acid and S-methyl-cysteine. The ascorbic acid is used to combat periodontal disease.

20 U.S. Patent No. 4,772,591 relates to a method for accelerated wound healing and discloses a composition very similar to that disclosed in U.S. Patent No. 4,590,067 discussed above. However, the calcium source is optional if the composition is to be given orally and the patient has sufficient dietary calcium. The ascorbic acid is used for curing periodontal disease and for certain healing properties. See also U.S. Patent No. 4,647,453.

25 Despite the work in stabilizing glucosamine sulphate that has gone before and the therapeutic importance of this compound, there remains the need to alternate methods of stabilizing glucosamine sulphate.

30 The present invention provides a composition which includes glucosamine sulphate in a highly storage-stable form.

35 In accordance with this aspect of the present invention, there is provided a storage-stable oral dosage formulation including a measured amount of glucosamine sulphate; and ascorbic acid and calcium carbonate in amounts effective to stabilize the measured amount of the glucosamine sulphate, substantially homogeneously admixed therewith.

40 Also in accordance with this aspect of the present invention, there is provided a storage-stable oral dosage formulation including a measured amount of glucosamine sulphate; an ascorbic acid selected from the group consisting of crystalline ascorbic acid

or a physiologically acceptable crystalline ascorbate salt, and calcium carbonate the ascorbic acid and the calcium carbonate being present in an amount effective to stabilize the measured amount of the glucosamine sulphate, substantially homogeneously admixed therewith.

The formulation thus produced has several advantages. First, it has enhanced storage stability and adequately addresses both the hygroscopic and oxidative tendencies of glucosamine sulphate. While not wishing to be bound by any particular theory of operability, it is believed that the ascorbic acid acts as an antioxidant and the carbonate acts as a desiccant.

In a particularly preferred aspect of the present invention, the formulation includes either crystalline ascorbic acid or a physiologically acceptable crystalline ascorbate salt. The use of this form of ascorbic acid provides additional lubricating properties which allow for the manufacture of an oral dosage form without the need to resort to additional tableting adjuvants. This allows for a reduced production cost, eliminates the need to employ ingredients which may adversely affect the health of a patient to which they are administered, and reduces the possibility of reactions between ingredients which may adversely effect the storage stability of the glucosamine sulphate. Also, the unique combination of ingredients of this invention provides a safe system for the patient, as the calcium carbonate tends to neutralize the ascorbic acid when an oral dosage form of the present invention is ingested.

It is also an object of the present invention to provide a method of stabilizing an oral dosage form of glucosamine sulphate that results in a product of enhanced storage stability.

In accordance with this aspect of the present invention, there is provided a method of stabilizing an oral dosage form of glucosamine sulphate which includes the steps of providing a measured amount of glucosamine sulphate, admixing, substantially homogeneously therewith, ascorbic acid and calcium carbonate in amounts effective to stabilize the measured amount of the glucosamine sulphate ; and forming the admixture into an oral dosage form, having enhanced storage stability.

Also in accordance with this aspect of the present invention, there is provided a method of stabilizing an oral dosage form of glucosamine sulphate including the steps of providing a measured amount of glucosamine sulphate, admixing, substantially homogeneously therewith, ascorbic acid selected from the group consisting of crystalline ascorbic acid and a physiologically acceptable crystalline ascorbate salt, and calcium carbonate said ascorbic acid on said calcium carbonate being provided in an amount effective to stabilize the measured amount of the glucosamine sulphate ; and forming the admixture into an oral dosage form, having enhanced storage

stability.

The method provides a protocol by which 5 glucosamine sulphate containing oral dosage forms having enhanced storage stability may be manufactured.

As previously noted, glucosamine sulphate synthesis was described by Breuer in 1898 (Chem. 10 Ber. 31, 2197) and an industrial method is described in U.K. Patent No. 1,056,331, U.S. Patent No. 3,683,076 and Swiss Patent No. 525,861, the disclosures of which methods are hereby incorporated by reference. Glucosamine sulphate prepared in accordance with Swiss Patent No. 525,861 generally involves liberation of the glucosamine from its hydrochloride in an aqueous-alcoholic medium, in the presence of triethylamine, and subsequent treatment of the obtained base in an acetone medium with the stoichiometric quantity of concentrated sulphuric acid to give the glucosamine sulphate. In the Swiss patent cited above, ethyl ether is used, but in industrial preparations on a large scale, it is preferred to use acetone which is much less dangerous and moreover, 15 yields a product with the same characteristics as those described in the Swiss patent.

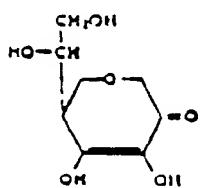
Ascorbic acid (Vitamin C) can be obtained in reduced form from a number of commercial sources. While the present invention includes the use of 20 commercial ascorbic acid in formulating the storage-stable dosage formulations of the present invention, it should be recognized that conventional dry powder Vitamin C formulations have certain limitations. For example, the flow characteristics of two such products are impaired because of the recognized hygroscopicity of ascorbic acid (see, for example, Pipher U.S. 25 Patent No. 2,846,353, at column 2, lines 21-27). In addition, it has long been known that ascorbic acid is a reducing agent which, upon oxidation (e.g., during 30 storage at elevated temperatures), is susceptible to discoloration (see, for example, Magid U.S. Patent No. 3,493,659, at column 1, lines 21-23). For these 35 reasons, the preferred formulation in accordance with the present invention includes the use of crystalline 40 ascorbic acid or crystalline physiologically acceptable ascorbate salts.

The crystalline ascorbic acid materials referred to 45 herein include both ascorbic acid *per se*, and the physiologically acceptable cationic ascorbate salts, e.g., sodium ascorbate, calcium ascorbate, and magnesium ascorbate. The crystalline ascorbic acid materials are generally rhomboid shaped, plate-like 50 crystals which may have particle sizes passing anywhere from 200 to 10 mesh screens, with crystals of medium-fine grade (30-80 mesh) being particularly preferred. The crystals may be directly incorporated in the dry powder formulations of the present invention.

The crystalline ascorbic acid materials utilized 55 herein are commercially available substances which may be produced by the hydrogenation of D-glucose

to D-sorbitol, followed by the microbial oxidation to L-sorbose, carboxylation to diacetone-2-keto-L-galonic acid, and conversion to ascorbic acid by heating with hydrogen chloride. The ascorbate salts may of course be produced directly from the acid if desired.

The structure of the crystalline ascorbic acid materials utilized in accordance herewith has been elucidated in the literature (see "The Crystal Structure of L-Ascorbic Acid 'Vitamin C'", J. Hvoslef, *Acta Chemica Scandinavica*, 18, No. 3, 1964, pp. 841-842). It has thus been shown by Fourier mapping that crystalline ascorbic acid possesses the following, generally accepted structural formula :



The 5-member ring is substantially planar. The material has a monoclinic crystalline structure, usually in plate-like form with occasional needles, four molecules of the ascorbic acid defining a unit cell. Two unit cells form pairs in pseudo-symmetrical order, whereby the molecules as well as the unit cells are connected by hydrogen bonding. The resultant planar crystals are thus slidable relative to each other, permitting them to act as a dry lubricant to impart free flowability to powders which otherwise tend to cake, stick or clump during encapsulation or tableting thereof.

In addition, the individual ascorbic acid (or ascorbate) crystals are readily fracturable due to the lack of extreme density and strength within the individual crystal structures. It is thus possible to break and compact the individual crystals upon subjecting the dry powder formulations containing the same to compressive forces during encapsulation or tableting. The dry powder formulation incorporating the crystalline ascorbic acid materials are thus readily compressible, as well as free flowing.

It is further believed that the crystalline synthetic ascorbic acid materials utilized in accordance with the present invention are more stable than natural ascorbic acid crystals or the amorphous, fine powder ascorbic acid utilized in conventional multi-vitamin formulations. Materials of these latter types have been described as being subject to oxidation upon exposure to air and light (see the *Merck Index*, 8th Edition, 1968, p. 105). The synthetic crystalline ascorbic acid utilized in the formulations hereof may, because of the existence of hydrogen bonding in the crystal, be less susceptible to autoxidation to dehydro-ascorbic acid and thus exhibit superior stability.

The incorporation of crystalline ascorbic acid into

dry powder formulations having improved flow and compressibility characteristics was described in U.S. Patent No. 4,454,125 which is incorporated herein by reference thereto.

According to *The Merck Index*, 9th edition, calcium carbonate exists in nature and the minerals aragonite, calcite and vaterite. Calcium carbonate is generally an odorless, tasteless powder or crystal which is practically insoluble in water. Calcium carbonate is commercially available from a number of sources.

The amount of calcium carbonate and ascorbic acid used in accordance with the present invention depends upon the amount of glucosamine sulphate to be delivered by the individual oral dosage. In all cases, there should be an amount of ascorbic acid and calcium carbonate sufficient to be effective to stabilize the measured amount of glucosamine sulphate to be delivered by the dosage. While not wishing to be bound by any particular theory of operation, it is believed that the ascorbic acid should be present in an amount effective to prevent the oxidation of the glucosamine sulphate and the calcium carbonate should be present in an amount effective to dessicate the glucosamine sulphate. If a conventional dry powder ascorbic acid is used in the practice of the present invention, it is advisable to use additional calcium carbonate to compensate for the hygroscopic properties thereof.

The amount of glucosamine sulphate used in the practice of the present invention depends upon the reason for prescribing and/or dispensing thereof. Typical single oral dosages could include from between about 50 mg to about 1500 mg. In preferred formulations, between about 100 mg and about 1000 mg may be used. In a more preferred embodiment of the present invention between about 200 mg and about 500 mg are used. Most preferably, the formulation in accordance with the present invention includes about 400 mg of glucosamine sulphate.

The amount of ascorbic acid useful in accordance with the present invention should be at least about 25 mg per 100 mg of glucosamine sulphate. In a preferred embodiment of the present invention, the amount of ascorbic acid should be between about 25 mg and 100 mg and more preferably about 75 mg per 100 mg of glucosamine sulphate.

The amount of calcium carbonate useful in accordance with the present invention should be at least about 35 mg per 100 mg of glucosamine sulphate. In a preferred embodiment in accordance with the present invention, the amount of calcium carbonate should be between about 37 mg and about 100 mg and more preferably about 75 mg per 100 mg of glucosamine sulphate.

It may be acceptable to add tableting adjuvants to help the flowability of the materials, their compaction, color, taste, binding and the like. However, the inclu-

sion of these ingredients should be limited to those which will not adversely effect the health of the patient to which they are administered or complicate the stabilization of the glucosamine sulphate.

Conventional tableting adjuvants and the conventional amounts used are described in Lieberman et al., Pharmaceutical Dosage Forms-Tablets, volume 1, 2d Ed., published by Marcel Dekker, Inc., in 1989, the text of which is hereby incorporated by reference. Tableting adjuvants clearly do not include other "active" ingredients such as the amino acids described in the 4,772,591 patent discussed previously.

In a preferred embodiment in accordance with the present invention, the use of crystalline ascorbic acid or a physiologically acceptable crystalline ascorbic salt in the formulation eliminates the need for such adjuvants.

The present invention includes the realization that the stabilization of glucosamine sulphate will require a compound solution involving a plurality of ingredients working in concert. The invention also includes an understanding of the nature of the instability of glucosamine sulphate and the development of a protocol and formulation whereby stability may be enhanced. By the practice of the present invention, the shelf life of glucosamine sulphate capsules may be extended from about three months to an expected 1 to 3 years. This allows for large scale production to be commercially feasible.

The method in accordance with the present invention involves providing a measured amount of glucosamine sulphate and homogeneously admixing therewith, an appropriate amount of stabilizing ingredients. Thus, once the amount of glucosamine sulphate to be delivered in each dosage has been determined and a sufficient amount of glucosamine sulphate raw material has been provided to accommodate the desirable number of dosage units to be produced, an effective amount of ascorbic acid and calcium carbonate are admixed substantially homogeneously therewith.

The term "effective amount" means enough ascorbic acid and calcium carbonate to effectively stabilize the measured amount of the glucosamine sulphate.

The mixture is then formed into one, or a plurality of individual oral dosage forms including capsule, tablets, suspensions and the like, having enhanced storage stability.

In a most preferred embodiment in accordance with the present invention, the oral dosage form is a capsule.

The foregoing will be better understood with reference to the following example. The example is for purposes of illustration and is not to be considered limiting as to the scope and nature of the present invention.

### EXAMPLE I

5                   22.857 Kg of glucosamine sulphate (Pfansfiehl  
Labs, Inc. of Waukegan, Ill, Lot No. 19470A) 17.142  
Kg of crystalline ascorbic acid (Hoffman-LaRoche,  
Nutley, NJ Lot No. 276119) and 17.142 Kg of extra  
heavy precipitated calcium carbonate (White Pigment  
10                   Corp., Florence, VT, Lot No. 9257) were used. The  
glucosamine sulphate was added to a 10 cu.ft. Patterson-Kelly twin shell tumble blender and tumbled for  
approximately 10 min. to break up any agglomerates.  
15                   The planar crystalline ascorbic acid is then added and  
the two components are mixed for approximately an  
additional 20 min. The extra heavy precipitated cal-  
cium carbonate is then added and mixing is con-  
ducted for approximately an additional 45 min. The  
20                   resulting admixture was loaded into the powder hop-  
per of a Zanasi AZ-20 intermittent motion capsule fil-  
ling machine in batches of 20 kg. The 6 powder  
dosators and pistons were treated with a 3/1000 mm  
chrome/nickel/boron coating and polished with  
25                   diamond grit by Isometric Microfinishing Co. in Edi-  
son, NJ for increased lubricity. Dosators are set at 2.1  
cm, powder pan set at 5.5 cm and dosator compres-  
sion set at "000". Room humidity must be kept be-  
tween 30-45% at 62-66°F. Capsules are filled at a rate  
30                   of 14,300 per hour to a fill weight of 1.0 gm into 2 piece  
hard gelatin capsules of size "00" from Pharmaphil  
Corp., Windsor, Canada.

35                   The principles, preferred embodiments, and  
modes of operation of the present invention have  
been described in the foregoing specification. The  
invention which is intended to be protected herein,  
however, is not to be construed as limited to the par-  
ticular embodiments disclosed, since these are to be  
regarded as illustrative rather than restrictive. Vari-  
40                   ations and changes may be made by others without  
departing from the spirit and scope of the invention.

### Claims

45                   1. A method of stabilizing an oral dosage form of  
glucosamine sulphate comprising providing a  
measured amount of glucosamine sulphate and  
forming said glucosamine sulphate into an oral  
dosage form, said method characterized by  
50                   admixing, substantially homogeneously with said  
glucosamine sulphate, ascorbic acid and calcium  
carbonate in amounts effective to stabilize said  
measured amount of said glucosamine sulphate  
so as to form said oral dosage form having en-  
hanced storage stability.

55                   2. The method of stabilizing an oral dosage form of  
glucosamine sulphate according to Claim 1,  
characterized by said ascorbic acid is present in  
an amount of at least about 25 mg per 100 mg of

glucosamine sulphate.

3. The method of stabilizing an oral dosage form of glucosamine sulphate according to Claim 2, characterized by said ascorbic acid being present in an amount of between about 25 mg and about 100 mg per 100 mg of said glucosamine sulphate.

4. The method of stabilizing an oral dosage form of glucosamine sulphate according to Claim 3, characterized by said ascorbic acid being present in an amount of about 75 mg per 100 mg of said glucosamine sulphate.

5. The method of stabilizing an oral dosage form of glucosamine sulphate according to Claim 1 or 2, characterized by said ascorbic acid being crystalline ascorbic acid or a physiologically acceptable crystalline ascorbate salt.

6. The method of stabilizing an oral dosage form of glucosamine sulphate according to Claim 1, 2, or 3, characterized by said calcium carbonate being present in an amount of at least about 35 mg per 100 mg of said glucosamine sulphate.

7. The method of stabilizing an oral dosage form of glucosamine sulphate according to Claim 6, characterized by said calcium carbonate being present in an amount of between about 37 mg and about 100 mg per 100 mg of glucosamine sulphate.

8. The method of stabilizing an oral dosage form of glucosamine sulphate according to Claim 7, characterized by said calcium carbonate being present in an amount of about 75 mg per 100 mg of glucosamine sulphate.

9. A storage-stable oral dosage formulation of a measured amount of glucosamine sulphate characterized by ascorbic acid and calcium carbonate in amounts effective to stabilize said measured amount of said glucosamine sulphate, substantially homogeneously admixed therewith.

10. The storage-stable oral dosage formulation according to Claim 9, characterized by said ascorbic acid being present in an amount of at least about 25 mg per 100 mg of said glucosamine sulphate.

11. The storage-stable oral dosage formulation according to Claim 10, characterized by said ascorbic acid being present in an amount of between about 25 mg and about 100 mg per 100 mg of said glucosamine sulphate.

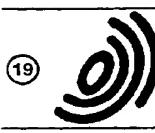
12. The storage-stable oral dosage formulation according to Claim 11, characterized by said ascorbic acid being present in an amount of about 75 mg per 100 mg of glucosamine sulphate.

13. The storage-stable oral dosage formulation according to Claim 9, 10 or 11, characterized by said ascorbic acid being crystalline ascorbic acid or a physiologically acceptable crystalline ascorbate salt.

14. The storage-stable oral dosage formulation according to Claim 9, 10 or 11, characterized by said calcium carbonate being present in an amount of at least about 35 mg per 100 mg of said glucosamine sulphate.

15. The storage-stable oral dosage formulation according to Claim 14, characterized by said calcium carbonate being present in an amount of between about 37 mg and about 100 mg per 100 mg of said glucosamine sulphate.

16. The storage-stable oral dosage formulation according to Claim 15, characterized by said calcium carbonate being present in an amount of about 75 mg per 100 mg of said glucosamine sulphate.



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



⑪ Publication number : **0 444 000 A3**

⑫

## EUROPEAN PATENT APPLICATION

⑯ Application number : **91850031.5**

⑮ Int. Cl.<sup>5</sup> : **A61K 31/70, A61K 9/48,  
A61K 47/02, A61K 47/22**

⑯ Date of filing : **12.02.91**

⑯ Priority : **22.02.90 US 483572**

⑰ Applicant : **Health Maintenance Programs, Inc.  
7 Westchester Plaza  
Elmsford, New York 10523 (US)**

⑯ Date of publication of application :  
**28.08.91 Bulletin 91/35**

⑰ Inventor : **Demopoulos, Harry Byron  
24 Sycamore Road  
Scarsdale, N.Y. 10583 (US)**

⑯ Designated Contracting States :  
**AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

⑰ Representative : **Kristiansen, Alf P. et al  
Albijn West AB Stora Nygatan 15 Box 142  
S-401 22 Göteborg (SE)**

⑯ Date of deferred publication of search report :  
**23.10.91 Bulletin 91/43**

⑯ Storage-stable glucosamine sulphate oral dosage forms and methods for their manufacture.

⑯ The present invention relates to storage-stable glucosamine sulphate oral dosage forms including calcium carbonate and ascorbic acid. The invention also relates to the methods of production of these oral dosage forms.

EP 0 444 000 A3

Jouve, 18, rue Saint-Denis, 75001 PARIS



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 91 85 0031

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. CL.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D, Y	EP-A-0 178 602 (PERITAIN, LTD) * * Page 1, lines 9-15; page 4, line 11 - page 5, line 2; page 5, lines 27-30; page 9, line 24 - page 10, line 30; pages 24,25, example 11; claims 5,8,9 * & US-A-4 772 591 (L.F. MEISNER) * ---	1-3,5-7 ,9-11, 13-15	A 61 K 31/70 A 61 K 9/48 A 61 K 47/02 A 61 K 47/22
Y	US-A-4 642 237 (V.A. DE STEFANIS) * Column 1, lines 6-11; column 3, lines 5-26; column 3, example 1; claim 1 *	1-3,5-7 ,9-11, 13-15	
D, A	EP-A-0 214 642 (ORION-YHTYMA OY FERMION) * Column 1, line 14 - column 2, line 16; claims 1,2 *	1-16	
A	EP-A-0 264 259 (TAISHO PHARMACEUTICAL CO., LTD) * Page 2, lines 29-37; pages 2,3, example 3 *	6-8,14- 16	
			TECHNICAL FIELDS SEARCHED (Int. CL.5)
			A 61 K C 07 H
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	02-08-1991	BOULOIS D.J-M.	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone	T : theory or principle underlying the invention		
Y : particularly relevant if combined with another document of the same category	E : earlier patent document, but published on, or after the filing date		
A : technological background	D : document cited in the application		
O : non-written disclosure	L : document cited for other reasons		
P : intermediate document	& : member of the same patent family, corresponding document		